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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/079,241	02/20/2002	Holly Hogrefe	25436/2155	7186

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EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/079,241	HOGREFE ET AL.	
	Examiner	Art Unit	
	Richard G Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *64-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *64-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants cancellation of claims 1-3, 6, 9-15, 19 and 21-23 and the addition of new claims 64-87, in the paper of 2/17/2004, is acknowledged. Claims 24-27 and 31-87 are still at issue and are present for examination.

Claims 24-27 and 31-63 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Objections

Claim 72 is objected to because of the following informalities:

Claim 72 recites "mutant KDO DNA polymerase". This should be "mutant KOD DNA polymerase".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 69-74 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 69-74 are indefinite in that they each refer to an enzyme mixture of claim 68, and appear to further limit the claimed genus, however the extent to which the genus is further limited is unclear. For instance, claim 69 is drawn to the enzyme

mixture of claim 68, wherein said mutant DNA mutant Pfu DNA polymerase contains a mutation at an amino acid position selected from the group consisting of at D405, Y410, T542, D543, K593, Y595, Y385, G387 or G388. The problem is that claim 69 makes no limitation that the claimed mutant polymerase must be a mutant Pfu DNA polymerase, thus in effect claim 69 is drawn to the enzyme mixture of claim 67, wherein said mutant DNA polymerase comprising a mutation in its partitioning domain or polymerase domain is a mutant Pfu DNA polymerase, KOD DNA polymerase, or JDF-3 DNA polymerase, wherein said mutant DNA mutant Pfu DNA polymerase contains a mutation at an amino acid position selected from the group consisting of at D405, Y410, T542, D543, K593, Y595, Y385, G387 or G388. Thus claim 69 still encompasses the specific amino acid mutants of Pfu as well as partitioning domain or polymerase domain mutants of KOD DNA polymerase, or JDF-3 DNA polymerase. For the purpose of advancing prosecution claim 69 is interpreted as if it further limited the claim from which it depends such that it must be a mutant Pfu DNA polymerase with one of the specified mutations.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65, 66, 68, 69, 73, 74, 76-81, 83 and 84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The rejection is stated in the previous office action, as it applied to claims 3 and 15. In response to this rejection applicants have cancelled claims 3 and 15 and added new claims 64-87 and traverse the rejection as it applies to the newly added claims.

Applicants submit that a deposit of the referred to bacterial DNA polymerases is not required because the DNA polymerases claimed are known in the art. Applicants further submit that the specification provides accession number for each of the claimed DNA polymerases, their encoding DNA as well as a corresponding reference. Applicants conclude that deposits are not required because one skilled in the art could make or use the invention defined in and commensurate with the claims without access to specific biological material.

Applicants argument is not found persuasive because while as stated in the MPEP Section 2402:

Biological material need not be deposited unless access to such material is necessary for the satisfaction of the statutory requirements for patentability under 35 U.S.C. 112. If a deposit is necessary, it shall be acceptable if made in accordance with these regulations. Biological material need not be deposited, *inter alia,* if it is **known** and **readily available to the public or can be made or isolated without undue experimentation**. Once deposited in a depository complying with these regulations, a biological material will be considered to be readily available even though some requirement of law or regulation of the United States or of the country in which the depository institution is located permits access to the material only under conditions imposed for safety, public health or similar reasons. Applicants argue that the

polymerases of the rejected claims are known, however it remains as to whether these polymerases are **readily available to the public or can be made or isolated without undue experimentation.**

As previously stated, the DNA polymerases are not fully disclosed, nor have they been shown to be publicly known **and freely available**. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the DNA polymerases or the bacterium from which they are isolated. Accordingly, it is deemed that a deposit of these polymerases or bacterium should have been made in accordance with 37 CFR 1.801-1.809.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 64-69, 75, 82, 83 and 85-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barnes et al. (U.S. Patent No. 5,436,149) and Komori et al. (Protein Engineering, Vol 13. No. 1, pages 41-47, 2000).

The rejection was stated in the previous office action as it applied to claims 1-3, 10, 11, 13, 14, 19 and 21-23 and repeated below for applicants convenience.

Barnes teach a number of thermostable DNA polymerase mutants and formulations of the taught DNA polymerases and other thermostable DNA polymerases,

which formulation of enzymes are capable of efficiently catalyzing the amplification by PCR of unusually long and faithful DNA products. Barnes specifically teach a formulation of thermostable DNA polymerases comprising at least one thermostable DNA polymerase lacking 3'-exonuclease activity and at least one thermostable DNA polymerase exhibiting 3'-exonuclease activity, wherein the thermostable DNA polymerase exhibiting 3'-exonuclease activity is a variant of the *Pfu* DNA polymerase wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated.

Komori et al. teach the functional interdependence of DNA polymerizing and 3'-5' exonucleolytic activities in *Pyrococcus furiosus* (*Pfu*) Polymerase I. Specifically, Komori et al teach a number of *Pfu* DNA polymerase mutants which affect both the DNA polymerizing and/or the 3'-5' exonucleolytic activity in varying amounts. Komori et al. specifically teach mutant *Pfu* DNA polymerases in which the Asp 405 has been replaced by alanine, D405A, and glutamate, D405E. Each of these mutants have a greater then 100-fold and greater then 20-fold decrease, respectively, in the polymerizing activity of the mutant DNA polymerase, relative to the wildtype *Pfu* DNA polymerase. These mutants further have an approximate 10-fold decrease in the exonuclease activity. Thus each of the mutants created by Komori et al. have an approximate 50-fold and 2-fold increase, respectively, in the ratio of 3'-exonucleolytic activity to polymerizing activity relative to the wildtype *Pfu* DNA polymerase.

One of ordinary skill in the art at the time of filing would have been motivated to use either of the *Pfu* DNA polymerase mutants, D405A and D405E, taught by Komori et

al. in the formulation taught by Barnes et al. to catalyze the amplification by PCR of unusually long and faithful DNA products. One would have been further motivated to include in the above formulation a PCR enhancing factor or an additive, as the purpose of the taught formulation is for PCR and package this formulation as a kit. The motivation for using the *Pfu* DNA polymerase mutants taught by Komori et al. comes from Barnes who teach that the thermostable DNA polymerase exhibiting 3'-exonuclease activity of the DNA polymerase formulation is preferably a variant of the *Pfu* DNA polymerase, wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated. The mutants taught by Komori et al. are such variants of the *Pfu* DNA polymerase, wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated. The reasonable expectation of success is high as both Barnes and Klomori et al. teach a number of thermostable DNA polymerases for use in the taught formulation, and Komori et al. specifically teach the *Pfu* DNA polymerase, wherein the DNA polymerase activity of said *Pfu* DNA polymerase has been diminished or inactivated. It is acknowledged that the mutant *Pfu* DNA polymerases taught by Komori et al. in addition to having a diminished or inactivated DNA polymerase activity also have a reduced 3'- exonucleolytic activity, however as the specific mutants taught by Komori et al. actually have an increase in the ratio of 3'-exonucleolytic activity to DNA polymerizing activity, they would remain useful in the formulation of Barnes, as the presence of the 3'-exonucleolytic activity is the reason for addition of the second DNA polymerase of the formulation. This is further supported by the teachings and claims of Barnes who teach that the ratio of the

"polymerase without 3'-exonucleolytic activity" to the "polymerase with 3'-exonucleolytic activity, wherein the polymerase activity is reduced or diminished" is high (i.e. from 10 to 2000 units to 1 unit), suggesting that the only functional property of the second polymerase that is important is the presence of the 3'-exonucleolytic activity, and that based on the ratios of the taught polymerase formulations, a slight decrease in the level of 3'-exonucleolytic activity can be accounted for by adjusting the ration of polymerases to remain within the level suggested by Barnes.

In response to this rejection, applicants have cancelled claims 1-3, 10, 11, 13, 14, 19 and 21-23 and added new claims 64-87 and traverse the rejection as it applies to the newly added claims.

Applicants submit applicants interpretation of what each of the references, Komori et al. and Barnes et al., teach and applicants submit that it is essential for the second DNA polymerase of the present invention to have a "reduced DNA polymerase activity" as required in claims 64-87. Applicants submit that neither Komori et al. or Barnes et al. teach the importance of having a reduced DNA polymerization activity.

Applicants argument, particularly as it applies to applicants interpretation of the reference of Barnes et al. is not found persuasive as applicants attention is drawn to claim 8 of the patent of Barnes et al. which recites "A formulation of thermostable DNA polymerases as set forth in claim 6, wherein the at least one thermostable DNA polymerase exhibiting 3'-exonuclease activity is selected from the group consisting of Pfu polymerase from Pyroccus furiosus, the Vent DNA polymerase from Thermococcus litoralis, a variant of the Pfu DNA polymerase wherein the DNA

polymerase activity of said Pfu DNA polymerase has been diminished or inactivated, or a variant of the Vent DNA polymerase wherein the DNA polymerase activity of said Vent DNA polymerase has been diminished or inactivated". Thus Barnes specifically teach an embodiment of the claimed formulation encompasses a Pfu DNA polymerase which has 3' exonuclease activity while its polymerase activity is diminished or inactivated.

Applicants argument that Barnes et al. does not provide any teaching as to why a Pfu DNA polymerase mutant with diminished or inactivated DNA polymerase activity is desired is acknowledged however not found relevant as Barnes teach the use of such a mutant Pfu DNA polymerase, regardless of motivation as taught by Barnes et al. or the instant inventors.

Applicants argument as it applies to claims 64 and 85 and their dependent claims, that the first enzyme is limited to an Archael DNA polymerase i.e., an exo+ DNA polymerase and Barnes et al. do not teach or suggest the combination of an exo+ DNA polymerase with another exo+ DNA polymerase with reduced polymerization activity as claimed in the claims and Komori et al. do not teach an enzyme mixture, is unclear and not found persuasive. Applicants attention is directed to referred to claims 64 and 85 which are each drawn to an enzyme mixture comprising an Archael DNA polymerase and a mutant Archael DNA polymerase. With respect to the teachings of Komori et al. it is agreed that Komori et al. do not teach an enzyme mixture, but as previously stated and stated above, Komori et al. is relied upon for its teaching of the specific mutant Pfu DNA polymerase, not an enzyme mixture.

Thus claims 64-69, 75, 82, 83 and 85-87 are made obvious over Barnes et al. and Komori et al.

Double Patenting

Applicants comments in response to the previous statutory type double patenting rejection regarding the canceling of the subject matter of claims 1-3, 6, 9-11, 13-15, 19 and 21-23 are acknowledged, however it is further acknowledged that applicants along with the cancellation of claims 1-3, 6, 9-11, 13-15, 19 and 21-23, applicants added new claims 64-87 drawn to overlapping subject matter, thus necessitating a provisional nonstatutory double patenting rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 64-87 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, 9-14, 18, 20-22 and 36-51 of copending Application No. 10/035,091. Although the conflicting claims are not identical, they are not patentably distinct from each other because the

claimed enzyme mixtures of the instant application, comprising a first enzyme and a second enzyme wherein said first enzyme comprises a Archael DNA polymerase and said second enzyme is a mutant Archael DNA polymerase comprising a 3'-5' exonuclease activity and a reduced polymerization activity and having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon are anticipated by and thus obvious over the corresponding claims of copending Application No. 10/035,091, drawn to a enzyme mixture comprising a first enzyme and a second enzyme wherein said first enzyme comprises a DNA polymerization activity and said second enzyme is a mutant Pfu DNA polymerase having a mutation at an amino acid position selected from the group consisting of D405, Y410, T542, K593, Y595, Y385, Y387, and G388 and those further limited claims dependent thereon.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

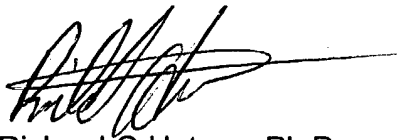
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (571) 272-0930. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on (571) 272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Richard G Hutson, Ph.D.
Primary Examiner
Art Unit 1652

rgh

4/8/2004